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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Appellant(s): Katherin Gordon et al.

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William G. Gosz
For Appellant

95-3206

EXAMINER'S ANSWER

This is in response to Appellants' Brief on appeal filed on June 29, 1994.

(1) Status of claims.

The statement of the status of claims contained in the Brief is correct.

(2) Status of Amendments After Final.

The Appellants' statement of the status of amendments after final rejection contained in the Brief is correct.

(3) Summary of invention.

The summary of invention contained in the Brief is correct.

(4) Issues.

The Appellants' statement of the issues in the Brief is correct.

(5) Grouping of claims.

The grouping of the claims in the Brief is correct.

(6) Claims appealed.

The copy of appealed claims in the Appendix to Appellants' Brief is correct.

(7) Prior Art of record.

The following is a listing of the prior art of record relied upon in the rejections of claims under appeal.

Andres et al., Experientia 42(6): 673-674 (1986)

Pennica et al., Nature 301: 214-222 (1983)

Chisari et al., Science 230: 1157-1160 (1985)

Campbell et al., Nucl. Acid Res. 12(22): 8685-8697 (1984)

Palmiter et al., Cell 41: 343-345 (1985)

Ross et al., Proc. Natl. Acad. Sci. 82: 5880-5884 (1985)

Stewart et al., Cell 38: 627-637 (1984)

(8) New prior art.

No new prior art has been applied in this Examiner's Answer.

(9) Grounds of rejection.

The following grounds of rejection are applicable to the appealed claims.

Claims 1, 2, 5-9 and 11, on appeal, stand rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to a DNA construct comprising a whey acidic protein (WAP) promoter.

The specification is not enabling for a DNA construct comprising all mammalian milk serum protein promoters. While the claims are directed to the use of all mammalian milk serum protein promoters, the specification only discloses the construction of fusion genes using a single mammalian milk serum protein promoter, i.e., the mouse WAP promoter. It is well known in the art that the level and specificity of expression of each individual transgene construct as well as the effects of its expression on the animal as a whole are not readily predictable due to uncontrollable factors such as the site of integration of the transgene. There is insufficient evidence in the specification which indicates that all mammalian milk serum protein promoters can be utilized with success for the production of all

foreign proteins in the mammary gland (and milk) of a transgenic mammal without undue experimentation. Accordingly, the disclosure is enabling only for claims limited to a DNA construct comprising a whey acidic protein promoter.

Claims 1, 2, 4 and 6-9, on appeal, stand rejected under 35 U.S.C. 103 as being unpatentable over Andres et al..

Andres et al. disclose a DNA construct comprising the human H-ras gene operably linked to the whey acidic protein promoter. Their teachings differ from the claimed invention in that the DNA construct does not further comprise the whey acidic protein signal sequence enabling secretion of the human H-ras protein. However, it would have been obvious for one of ordinary skill in the art to modify the DNA construct taught by Andres et al. by inserting into the construct the whey acidic protein signal sequence for the expected benefit of obtaining secretion of the human H-ras protein into milk, with a reasonable expectation of success. Thus the claimed invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary. In view of the clear prima facie case of obviousness made out over the references, the burden has shifted to Appellants to rebut the same with evidence of nonobviousness. However, the evidence relied on by Appellants taken as a whole is not effective for such purpose.

Claims 5 and 11, on appeal, stand rejected under 35 U.S.C. 103 as being unpatentable over Andres et al., as applied to claims 1-4 and 6-9 above, and further in view of Pennica et al. or Chisari et al..

Pennica et al. disclose a cDNA encoding human tissue plasminogen activator (tPA) and its expression in E. coli while Chisari et al. disclose a DNA segment encoding the hepatitis B surface antigen (HBsAg) and its expression in transgenic mice. Accordingly, the additional modification of the DNA construct taught by Andres et al. by substituting the DNA encoding human tPA or HBsAg (each containing its own signal sequence for secretion) for the

human H-ras gene would have been obvious to one of ordinary skill in the art. Thus the claimed invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary. In view of the clear prima facie case of obviousness made out over the references, the burden has shifted to Appellants to rebut the same with evidence of nonobviousness. However, the evidence relied on by Appellants taken as a whole is not effective for such purpose.

Claims 1, 2, 4-9 and 11, on appeal, stand rejected under 35 U.S.C. 103 as being unpatentable over Campbell et al., when taken with either Pennica et al. or Chisari et al., and further in view of any one of Palmiter et al., Ross et al. or Stewart et al..

Campbell et al. disclose the genes coding for the rat and mouse mammary tissue-specific whey acidic protein and their promoter regions. They do not specifically teach a DNA construct comprising a whey acidic protein promoter operably linked to a DNA sequence encoding a heterologous protein such as human tPA or HBsAg. However, at the time the claimed invention was made, Pennica et al. disclosed a cDNA encoding human tPA while Chisari et al. disclosed a DNA segment encoding HBsAg. Furthermore, Palmiter et al. reviewed the many studies on the tissue-specific expression of heterologous gene products in transgenic mice while Ross et al. and Stewart et al. each reported mammary tissue-specific expression of heterologous genes in transgenic mice. Accordingly, it would have been obvious for one of ordinary skill in the art to operably link the whey acidic protein promoter to a DNA sequence encoding human tPA or HBsAg in order to obtain a DNA construct useful for the expression and secretion of human tPA or HBsAg in the mammary tissue of a transgenic mammal, with a reasonable expectation of success. Thus the claimed invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary. In view of the clear prima facie case of obviousness made out over the references, the burden has shifted to

Appellants to rebut the same with evidence of nonobviousness. However, the evidence relied on by Appellants taken as a whole is not effective for such purpose.

(10) New ground of rejection.

This Examiner's Answer does not contain any new ground of rejection.

(11) Response to arguments

Response to Argument I

Appellants assert on page 5 of the Brief that the Examiner has criticized the Gordon Declaration as being based on "speculation" and "opinion". They further allege that "it is improper to dismiss the Gordon Declaration on this basis since the issue to be addressed is enablement, not obviousness" and that the enablement issue "is necessarily a subjective inquiry which is not always amenable to quantification by concrete supporting evidence" (pages 5-6 of the Brief). It is noted that in order for a declaration under 37 C.F.R. 1.132 to be given much weight, the statements made should be well supported by sound scientific principles and/or relevant experimental data. See MPEP 716. It is maintained that frequently, the issue of enablement may be resolved by performing appropriate experiments to demonstrate or support the scope of the invention being claimed and providing the data thus obtained as objective evidence. Moreover, while Appellants argued in their earlier Response filed September 8, 1993 that "it was reasonable to expect milk proteins to share similar regulatory mechanisms and regulatory sequences", they had not submitted any objective evidence (e.g., published reports on the comparisons of milk protein regulatory sequences, etc.,) to support such a statement or other assertions made in the Gordon Declaration.

Appellants then cite In re Wands in support of their statement that "Appellants are entitled to rely on what is disclosed in the specification, as

well as disclosures in the prior art" (page 7 of the Brief). Appellants further cite a publication by Henninghausen and Sippel as evidence that milk serum proteins other than the WAP protein were previously known and characterized (see lines 13-15 on page 7 of the Brief). The Examiner notes that the cited publication has not been previously made of record and is being considered only to the extent relied on in Appellants' argument. The publication by Henninghausen and Sippel is titled "Characterization and cloning of the mRNAs specific for the lactating mouse mammary gland". A review of the publication indicates that partial cDNAs for mouse caseins and WAP were isolated (see Table 1 on page 136 of the publication, for example). Firstly, it should be noted that caseins are not milk serum proteins (see page 4, lines 2-6 of the specification, for example). Furthermore, the statements made in the Brief and the Gordon Declaration regarding the predictability of the art and the non-obviousness of Appellants' claimed invention appear to be contradictory. While on one hand Appellants assert that "the level of skill in the field of biotechnology is relatively high..." (page 8 of the Brief), Appellants also point out in their rebuttal to the obviousness rejection that the reference, Campbell et al., cited in the rejection, "expressly do not in any way describe or identify the WAP promoter region of the genomic sequence, and there is no appreciation in the reference that the WAP promoter would have any utility for use in a DNA construct to express foreign proteins in the milk of a transgenic animal" (page 15 of the Brief). Thus, by the same token, even if the publication by Henninghausen and Sippel had in fact disclosed partial cDNAs for the mouse alpha-lactoalbumin gene, it is not sufficiently enabling for one skilled in the art, as of the effective filing date, to identify, clone, and utilize the promoter region of the alpha-lactoalbumin genomic sequence in the preparation of a DNA construct useful for the expression of a heterologous protein in the mammary gland of a transgenic mammal.

While the reduction to practice of a claimed invention is not a legal requirement under 35 U.S.C.112, an experimental demonstration as to how one actually makes and uses the claimed invention may be necessary when

dealing with a new and unpredictable art. In the instant case, Appellants' claimed invention is directed to a DNA construct useful for the expression of a heterologous protein in the mammary gland of a transgenic mammal. The animal system is a complex in vivo system and the production of transgenic animals is a highly unpredictable art. Moreover, as Appellants point out on page 11 of the Brief, even with a DNA construct comprising the WAP promoter (referring to the abstract by Andres et al.), it cannot be predicted that the specificity of expression of the individual transgene construct is restricted to the mammary gland.

Appellants then allege that the Examiner has not considered all the Wands factors other than the unpredictability factor (page 9 of the Brief). It is maintained that the Examiner has in fact considered all relevant factors (including the state of the art, the amount of experimentation, the degree of predictability, the amount of disclosure, etc.) and all evidence of record before arriving at the conclusion that the instant specification is enabling only for claims limited to the use of a WAP promoter.

Finally, Appellants present additional considerations and cite a U.S. patent on pages 9-10 of the Brief. The Examiner does not find those considerations relevant to the issue at hand. With regard to the cited patent, it should be noted that each case is examined upon its own merits. In re Durden, 226 USPQ 359, 362 (CAFC 1985). Furthermore, contrary to Appellants' allegation, the claims of '316 patent are limited to the use of a casein promoter as exemplified in the specification.

Response to Argument II

Contrary to Appellants' allegation on page 11 of the Brief, Andres et al. were indeed successful in obtaining mammary-gland expression of foreign DNA (see lines 6-8 of the abstract). Appellants' attention is directed to the claims at issue which are merely directed to a DNA construct. The claims are not directed to a method of tissue-specific expression or transformation, or

to a transgenic mammal per se. Moreover, there are no limitations on the level or tissue-specificity of expression of foreign gene recited in the claims. Appellants readily agree with the Examiner that the only difference between the DNA construct of the claimed invention and the construct disclosed by Andres et al. is the presence of a signal peptide sequence (page 11 of the Brief). It is noted that at the time the claimed invention was made, signal peptide sequences (of milk proteins as well as of other proteins) enabling the secretion of proteins were well known. Thus, if one of ordinary skill in the art so desired to have secretion of the recombinant proteins into milk, one of ordinary skill would have obviously included a signal peptide sequence into the DNA construct for the expected benefit of obtaining secretion of the recombinant proteins. The inclusion of one of the many well known signal sequences in a DNA expression construct (whether for expression in cells in culture or in a transgenic animal) would have been well within the ordinary skill of the art as of the effective filing date.

Appellants then assert that they were "the first to undertake this approach, i.e., Appellants were the first to appreciate that foreign proteins could be successfully expressed in the milk of a transgenic animal" (page 12 of the Brief). This argument is not persuasive for at least two reasons. Firstly, the claims at issue are not directed to transgenic animals. Moreover, transgenic mammals which produce foreign proteins in their milk are not described or enabled by the instant specification

Response to Argument III

Appellants argue that Pennica et al. do not suggest the use of tPA cDNA in developing a transgenic animal and that Chisari et al. do not suggest the use of hepatitis B virus surface antigen DNA for the production of foreign proteins in the milk of a transgenic mammal (page 14 of the Brief). In this regard, it is noted that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201

USPQ 67 (CCPA 1979). Furthermore, the test for combining references is not what the individual references themselves suggest but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. In re McLaughlin, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Thus, it is the Examiner's position that the combination of the disclosure of Andres et al. and that of Pennica et al or Chisari et al., when taken as a whole, would have reasonably suggested to one of ordinary skill in the art a DNA construct identical or similar to that claimed by Appellants. Appellants additionally assert that the expression of the antigen in Chisari et al. was not tissue specific. Again, Appellants are reminded that the claims at issue are directed to a DNA construct, and not to a transgenic mammal. See the discussion earlier.

Response to Argument IV

Appellants assert that Campbell et al. expressly do not in any way describe or identify the WAP promoter region of the genomic sequence (page 15 of the Brief). As stated above, a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests to one of ordinary skill in the art. Campbell et al. clearly disclose the genes coding for the rat and mouse mammary tissue specific WAP and their promoter regions. Appellants also acknowledge that Campbell et al. identified several potential regulatory sequences of the WAP gene (page 15 of the Brief). Thus, one of ordinary skill in the art would certainly have been motivated to identify the genomic sequences which are essential for mammary-gland specific expression. Appellants then point out the teachings of the tertiary references (page 16 of the Brief). It is maintained that the test of obviousness is not express suggestion of the claimed invention in any or all of the references, but rather what the references taken collectively would suggest to one of ordinary skill in the art presumed to be familiar with them. Furthermore, for the purpose of combining references, those references need

not explicitly suggest combining teachings, much less specific references. See In re Rosselet, 146 USPQ 183 and In re Nilssen, 7 USPQ2d 1500 (CAFC 1988). Accordingly, Appellants' arguments are not effective in overcoming the rejection.

(12) Conclusion

In summary, it is considered that claims 1, 2, 5-9 and 11, on appeal, are not enabled by the specification. Claims 1, 2, 4-9 and 11, on appeal, are unpatentable as being obvious as a whole to one of ordinary skill in the art at the time the claimed invention was made, as established by the references, and Appellants' arguments and evidence fail to persuade otherwise.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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